Isoflavone therapy for menopausal flushes: a systematic review and meta-analysis
Howes L G, Howes J B, Knight D C

CRD summary
The authors concluded that isoflavone supplementation may result in a slight to modest reduction in the number of daily menopausal flushes. Poor reporting of review methods, the lack of an assessment of study quality, and differences between the studies make it difficult to comment on the reliability of the authors’ conclusions.

Authors' objectives
To evaluate the effects of isoflavone supplementation on the number of daily menopausal flushes.

Searching
MEDLINE, PREMEDLINE, PubMed and the Cochrane CENTRAL Register were searched for published studies; the search terms were stated but the search dates were not. In addition, the references of identified studies and recent reviews were screened. Foreign language studies were included if there was an English language abstract.

Study selection
Parallel-group randomised controlled trials (RCTs) that compared the effects of isoflavone supplementation (either soy or red clover products) with a non-isoflavone, non-oestrogenic control on the number of daily menopausal flushes were eligible for inclusion. Studies had to last at least 4 weeks and report the number and variance of flushes per day at baseline.

The duration of the included interventions ranged from 6 to 52 weeks; most studies lasted 12 weeks. Where reported, the calculated dose of aglycone isoflavone generally ranged from 40 to 80 mg/day. The mean daily number of flushes at baseline ranged from 0.7 to 13.7.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors stated that the studies were assessed for adequacy of description and comparability of the treatment groups at baseline. However, the results of this assessment were not reported. The authors did not state how the validity assessment was performed.

Data extraction
For each study, the mean difference in percentage change in the number of daily flushes between treatment groups was presented, together with the statistical significance.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The pooled effect size was calculated using the difference in percentage change in the number of daily flushes from baseline between treatment groups, divided by the pooled standard deviation. Fixed-effect (weighted integration model) and random-effects models were used. Data for the last time point were used. The average reduction from baseline in the placebo group was also calculated.

It appears that the $I^2$ method was used to assess statistical heterogeneity, but the method used was not explicitly reported. Separate analyses were conducted for studies of soy and red clover products. Univariate and multivariate weighted regression analyses were used to examine the influence of baseline flushes, isoflavone dose and duration of treatment; the studies were weighted by sample size.
The number of studies required to negate a statistically significant result (i.e. the fail-safe N) was calculated.

**Results of the review**

Seventeen RCTs (n=1,503) were included: 5 studies (n=458) of red clover and 12 studies (n=1,045) of soy.

The average percentage reduction in the number of daily flushes from baseline in the placebo group was -29% (range: -1 to -59).

 Isoflavone was associated with a statistically significant reduction in the number of daily flushes compared with control (effect size -0.28, 95% confidence interval, CI: -0.39, -0.18); significant heterogeneity was found (p<0.0001). The effect size remained significant when using a random-effects model (-0.49, 95% CI: -0.81, -0.17, p=0.001).

 Soy isoflavone was associated with a statistically significant reduction in the number of daily flushes compared with control; the effect size was -0.54 (95% CI: -0.96, -0.13, p=0.004) when using a random-effects model. There was no significant difference between red clover isoflavone and control; the effect size (random-effects model) was -0.35 (95% CI: -0.86, 0.14, p=0.082). No significant heterogeneity was found for either of these subgroup analyses. Effect sizes for soy interventions appeared to range from favouring isoflavones (4 studies), to no statistically significant difference (7 studies), to one study favouring placebo.

 Multiple regression analysis showed that a greater number of baseline flushes (p<0.0001) and increased isoflavone dose (p<0.0001) were associated with a greater response to treatment.

 Twenty studies would be required to negate the statistically significant result.

**Authors’ conclusions**

Isoflavone supplementation may result in a slight to modest reduction in the number of daily menopausal flushes, with greater reductions in women with a high number of daily flushes at baseline.

**CRD commentary**

The review question was stated clearly. Several relevant sources were searched but no adequate attempts were made to minimise language and publication bias; the authors did calculate the fail-safe N. The methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Since study validity was not assessed, the results from these studies and any synthesis may not be reliable. Statistical heterogeneity was assessed, the studies were pooled using meta-analysis, and some potential sources of heterogeneity were assessed. The presence of significant heterogeneity may suggest that it was not appropriate to pool the data. A lack of reporting of review methods, lack of an assessment of study quality, and differences between the studies make it difficult to comment on the reliability of the authors’ conclusions.

All three authors have undertaken consultancy work or been employed at one time by Novogen Pty Ltd, a manufacturer of red clover isoflavone supplements.

**Implications of the review for practice and research**

Practice: The authors stated that the review supports the North American Menopausal Society’s recommendation that ‘for women with frequent hot flashes, clinicians may consider recommending soy foods or soy isoflavone supplements’.

Research: The authors did not state any implications for further research.

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